Prevalence and incidence of intraventricular conduction delays and outcomes in patients with heart failure and reduced ejection fraction: Insights from PARADIGM-HF and ATMOSPHERE

Title: **Prevalence and incidence of intraventricular conduction delays and outcomes in patients with heart failure and reduced ejection fraction: Insights from PARADIGM-HF and ATMOSPHERE**

Running title QRS width and subsequent widening in HFrEF

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Word count: 7171 including title page, abstract, text, references, tables, and figures

Subject codes: heart failure, left bundle branch block, electrocardiography

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ABSTRACT

Background: The importance of significant (≥130 milliseconds [ms]) intraventricular conduction delay (IVCD), especially with left bundle branch block (LBBB) morphology, in patients with heart failure and reduced ejection fraction (HFrEF) is well recognized. However, less is known about the prevalence of other types of IVCD/BBB in HFrEF and little about the incidence of new IVCD/BBB and its relationship to outcomes in HFrEF. We addressed these questions in the PARADIGM-HF and ATMOSPHERE trials.

Methods: Incidence rates and risks of the primary composite outcome of cardiovascular (CV) death or HF hospitalization and all-cause mortality were estimated by use of Cox regression according to baseline QRS duration and morphology in 11,861 patients without an intracardiac device. The incidence of QRS-widening during follow-up was calculated in patients (n=7,888) with baseline QRS<130 ms, along with outcomes related to QRS-widening and predictors of QRS-widening.

Results: At baseline, 1,789 (15%) patients had LBBB, 524 (4%) RBBB, 454 (4%) non-specific IVCD, 2588 (22%), "mildly abnormal" QRS (110-129 ms) and 6506 (55%) QRS <110 ms. During a median follow-up of 2.5 years, the risk of the primary composite endpoint was higher among those with a wide QRS, irrespective of morphology: hazard ratios (95% CI) LBBB 1.36 (1.23, 1.50), RBBB 1.54 (1.31, 1.79), nonspecific IVCD 1.65 (1.40, 1.94) and QRS 110-129 ms 1.35 (95% CI 1.23, 1.47), compared with QRS duration <110 ms. During a median follow-up of 2.7 years, 1234 (16%) patients developed new-onset QRS-widening ≥130 ms (6.1 per 100 patient-years); incident LBBB occurred in 495 (6.3%) patients (2.4 per 100 patient-years). QRS 110-129 ms, lower LVEF and heart rate, older age and longer-duration HF were independent predictors of incident QRS-widening. New-onset QRS-widening occurred at a rate of 14.1 per 100 patient-years in patients with baseline QRS 110-129 ms (incident LBBB 5.9 per 100 patient-years). Incident

LBBB was associated with a higher risk of the primary outcome and all-cause mortality: adjusted HRs 1.42 (1.12, 1.82) and 1.42 (1.11, 1.82), respectively.

Conclusion: In patients with HFrEF, a wide QRS was associated with worse clinical outcomes irrespective of morphology. The annual incidence of new-onset LBBB, a potential indication for cardiac resynchronization therapy, was around 2.5%, and was associated with a higher risk of adverse outcomes, highlighting the importance of repeat ECG review in patients with HFrEF.

Keywords: heart failure, left bundle branch block, prognosis, cardiac resynchronization therapy, electrocardiography

Clinical Trial Registration: URL http://www.clinicaltrials.gov. Unique identifier NCT0083658 (ATMOSPHERE) and NCT01035255 (PARADIGM-HF).

INTRODUCTION

Intra-ventricular conduction delay (IVCD), particularly with a left bundle branch block (LBBB) morphology, results in a dyssynchronous electrical activation sequence of the heart.[1] LBBB is known to be associated with worse outcomes in patients with heart failure and reduced ejection fraction (HFrEF), and cardiac resynchronization therapy (CRT) reduces the risk of worsening heart-failure and improves survival in such patients with a QRS duration ≥130 milliseconds (ms).[2-7] Less is known about the prevalence and prognostic significance of right bundle branch block (RBBB) and non-specific IVCD in HFrEF. More importantly, very little is known about the incidence and clinical consequences of new-onset QRS widening in patients with HFrEF.[8, 9] This information is important as a new diagnosis of IVCD may be of prognostic importance and may identify an indication for CRT.

In the present study we examined the prognostic importance of prevalent and incident QRS widening to a duration of ≥130 ms using data from two HFrEF trials which included a broad spectrum of ambulatory patients receiving contemporary therapy. The trials had nearly identical enrollment criteria.

METHODS

The design, baseline characteristics and primary results of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart FailuRE Trial (ATMOSPHERE) are published.[10-14] Both trials were approved by the ethics committee at each study center. All patients provided written informed consent.

Study Patients: For the present study we included patients without a device (pacemaker, CRT or ICD) and a baseline QRS duration between 60 and 240 ms (Figure 1). For analyses of incident IVCD, we excluded all patients with QRS≥130 ms at baseline and identified those who developed QRS-widening (QRS ≥130 ms) at annual follow-up ECGs and subsequently grouped these patients according to QRS morphology: LBBB, RBBB or non-specific IVCD (ns IVCD) with the hierarchy of LBBB>RBBB>ns IVCD if several different morphologies were reported.

The inclusion criteria for PARADIGM-HF and ATMOSPHERE were similar and included: New York Heart Association (NYHA) functional class II-IV status, left ventricular ejection fraction (LVEF) ≤35% (initially ≤40% for PARADIGM-HF but changed to ≤35% by amendment), and a plasma B-type natriuretic peptide (BNP) ≥150 pg/mL or NT-proBNP ≥600 pg/mL). In both trials, patients who had been hospitalized for heart failure within the preceding 12 months could be enrolled with a lower natriuretic peptide concentration (BNP ≥100pg/ml or NT-proBNP ≥400pg/ml). Plasma NT-proBNP was measured in a core laboratory with the Roche Elecsys proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany), with a coefficient of variation <2.5% at all levels tested.

Patients were required to be taking an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at a dose equivalent to enalapril 10 mg daily for at least 4 weeks before

screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. The exclusion criteria included history of intolerance of an ACE inhibitor or ARB, symptomatic hypotension (or a systolic blood pressure <100 mmHg at screening/<95 mmHg at randomization), an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 (<40 ml/min/1.73 m^2 for ATMOSPHERE) , a serum potassium concentration >5.2 mmol/l at screening (>5.4 mmol/l at randomization) (<5.0 mmol/l and <5.2 mmol/l, respectively in ATMOSPHERE) or a history of angioedema.

Study Procedures: In both PARADIGM-HF and ATMOSPHERE, patients first received enalapril (5 or)10 mg twice daily (single-blind) [15] and then sacubitril/valsartan (single-blind) for an additional 4 to 6 weeks in PARADIGM-HF and aliskiren plus enalapril in ATMOSPHERE. In PARADIGM-HF Patients tolerating both drugs at target doses were randomly assigned to enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily, and in ATMOSPHERE, patients who tolerated both drugs were randomized in a 1:1:1 ratio to receive: i) combination of 5 or 10 mg enalapril twice daily and aliskiren 150 mg once daily (combination group); ii) aliskiren 150 mg once daily; iii) enalapril 5 or 10 mg twice daily.

Categorization of patients according to baseline ECG findings: The case report form in each study asked investigators to report QRS duration (in milliseconds, ms) and there was an additional question about QRS morphology (specifically whether there was RBBB or LBBB). The information collected was used to categorize patients by baseline QRS duration: QRS <110 ms (normal), QRS 110-129 ms (mildly abnormal) and ≥130 ms (prolonged). Individuals with QRS ≥130 ms were additionally categorized by QRS morphology (i.e. LBBB, RBBB, non-specific IVCD subcategories). This resulted in the following 5 groups overall - 1) normal QRS duration: <110 ms (irrespective of reported QRS morphology), 2) mildly abnormal IVCD: QRS duration 110-129 ms (irrespective of reported QRS

morphology 3) LBBB: QRS ≥130 ms + LBBB morphology, 4) RBBB: QRS ≥130 ms + RBBB morphology, and 5) ns IVCD: QRS ≥130 ms without either LBBB or RBBB reported.

Outcomes: In the present manuscript we focused on the primary endpoint of both trials which was the first occurrence of cardiovascular death or HF hospitalization, as well as each of the components separately. We also report death from any cause, which was a secondary endpoint in PARADIGM-HF and a pre-specified exploratory outcome in ATMOSPHERE, as well as the two major modes of cardiovascular death i.e. death due to worsening HF ("pump failure") and sudden cardiac death. All suspected HF hospitalizations and deaths in each trial were adjudicated by the same endpoint committee.

Statistical Analysis: Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Event rates are reported per 100 patient years of follow-up according to QRS duration and for those with QRS duration ≥130 ms additionally according to QRS morphology. Cox proportional hazard models were applied to calculate hazard ratios (HR) and cumulative event curves according to QRS morphology with patients with no intraventricular conduction delay as reference. The adjusted Cox regression models included information on age, sex, race (Caucasian vs. all other), geographical region, study drug, NYHA class, left ventricular ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate (eGFR), HF duration, ischaemic etiology, history of recent HF hospitalization and history of myocardial infarction. Log (-log(survival)) curves were used to evaluate the proportional hazards assumption. The assumption of linearity of continuous variables (age) was tested by including a variable of age squared. These were found to be valid unless otherwise specified. QRS duration at baseline as a continuous variable adjusted for other prognostic variables, is shown modelled as a restricted cubic spline (QRS duration 100 ms is the reference value). Predictors of new-onset QRS-widening were

analyzed in a logistic regression model with similar adjustments as the Cox regression model. All p values are two-sided, and a p value of <0.05 was considered significant. Analyses were performed using Stata version 14 (Stata Corp. College Station, Texas, USA).

RESULTS

Of the overall 11,861 patients in the analysis, 6506 participants (55%) had a normal QRS duration (<110 ms) and 2588 (22%) had a mildly abnormal QRS (110-129 ms). The remaining 2767 patients (23%) had an abnormally wide QRS (≥130 ms). Among these individuals, 1,789 (15% overall/65% of participants with QRS ≥130 ms) had LBBB, 524 (4%/19%) RBBB, and 454 (4%/16%) ns IVCD. The median (Q1, Q3) follow-up was 30 (20, 40) months.

Baseline Characteristics: Patients with wide QRS (≥130 ms) were, in general, older (65 years vs. 63 and 62 years for QRS 110-129 ms and QRS<110 ms, respectively), had a slightly lower systolic blood pressure (122 mmHg vs 123 mmHg and 124 mmHg), worse kidney function (median eGFR 69 vs. 71 and 72 ml/min/1.73 m^2), and longer duration of HF (>5 years in 32% vs. 29% and 21%) irrespective of morphology (Table 1).

Patients with LBBB were more likely to be women (30%) compared to RBBB (13%) or ns IVCD (20%) and older (66 years vs 65 vs 64 years). Patients with LBBB were less likely to have an ischaemic aetiology (49% vs. 64% vs 63%, respectively). NT-proBNP was highest, and LVEF lowest, in patients with the widest QRS or LBBB. Conversely, atrial fibrillation was less common in patients with the widest QRS or LBBB.

Outcomes according to baseline QRS duration and morphology: The primary composite outcome of HF hospitalization or cardiovascular death occurred in 1543 (24%) of patients with QRS<110 ms (reference), as compared to 826 (32%) patients with mildly abnormal QRS (110-129 ms), 937 (34%) patients with any QRS ≥130 ms, 168 (37%) patients with ns IVCD, 187 (35%) patients with RBBB, and 582 (33%) patients with LBBB (Table 2, Figure 2). In adjusted Cox regression analyses, this corresponded to significantly increased risk for those with QRS 110-129 ms (HR 1.35; 95% CI 1.23, 1.47), any QRS ≥130 ms (HR 1.44; 95% CI 1.32, 1.57), ns IVCD (HR 1.65; 95% CI 1.40, 1.94), RBBB (HR 1.54; 95% CI 1.31, 1.79) and LBBB (HR 1.36; 95% CI 1.23, 1.50).

All-cause mortality occurred in 19% of patients with QRS<110 ms as compared to 26% of those with QRS 110-129 ms, 27% of patients with any QRS ≥130 ms, 28% of patients with ns IVCD and 27% of patients with RBBB and 26% with LBBB. The risks in patients with a wider QRS remained significantly higher in adjusted analyses, using QRS<110 ms as the reference group (Table 2). When the two principal modes of death were examined, wide QRS was associated with a higher risk of both pump failure and sudden cardiac death. The increase in risk was numerically larger for pump failure death than for sudden death.

Incidence and predictors of QRS widening and subsequent outcomes: Among 7,888 patients without any type of intracardiac device, and ECG with QRS duration <130 ms at baseline, 1234 (16%) developed QRS widening to ≥130 ms detected during follow-up visits, of which 495 (6.3% overall, 40% of patients developing QRS widening to ≥130 ms), had LBBB morphology (Table 3, Figure 3). These numbers corresponded to event rates of 6,1 and 2.4 per 100 patient-years, respectively. In a multivariable analysis, the following were independently significant predictors of incident QRS widening to ≥130 ms: QRS 110-129 ms vs. <110 ms (OR 4.55 [3.98-5.19]), age per 5 year increase (OR 1.06 [1.03-1.10]), HF duration, 1-5 years vs. <1 year (OR 1.23 [1.05-1.44]), >5 years vs. <1 year (OR 1.29 [1.08-1.54]), LVEF per 1% decrease (OR 1.03 [1.02-1.05]), heart rate (per 5 bpm decrease) (OR 1.06 [1.02-1.09]), prior stroke (OR 0.77 [0.59-1.00]), see Table 5. Patients with incident QRS ≥130 ms had subsequently higher event rates of the primary composite outcome (13.9 vs 7.4 per 100 py) and all-cause mortality (13.0 vs. 4.4 per 100 py), respectively. In adjusted Cox regression analyses this yielded HRs of 1.49 (95% CI 1.25, 1.76) for the primary outcome and 1.69 (95% CI 1.43, 2.00) for all-cause mortality. A similar pattern was seen when restricting the comparison to new-onset LBBB vs no LBBB (Table 6). Modes of death (i.e. pump failure of sudden cardiac death) were not examined because of the small numbers of events.

DISCUSSION

There are two principal findings in this study.

First is the clear demonstration that each of RBBB and ns IVCD, which together accounted for about a third of patients with QRS duration ≥130 ms, were predictive of a higher risk of both cardiovascular death or heart failure hospitalisation and all-cause mortality, and remained so after adjustment for other predictors of worse outcomes, including natriuretic peptides. Indeed, the adjusted increments in risk were at least as high in patients with each of these two ECG findings as in patients with LBBB at baseline. Previous studies did not distinguish between these ECG patterns and/or did not have sufficient numbers patients or events to demonstrate the associations with worse non-fatal as well as fatal outcomes.[2, 7, 16-19] Additionally, limited adjustment was possible in prior series, especially for natriuretic peptide level, the most powerful prognosticator of all.

Second, in the present study, even patients with a "mildly abnormal" QRS (110-129 ms) had a substantially elevated risk, an important finding given that there were almost as many individuals in this category (22% of overall participants) as there were individuals with QRS duration ≥130 ms (23% of participants).

Collectively these findings, especially the latter, stand in stark contrast to the evidence that CRT is most clearly beneficial in HFrEF patients with a QRS duration ≥130 ms and a LBBB configuration (a Class I Level A recommendation in guidelines) and may even be harmful in individuals with a QRS duration <130 ms.[20] Possibly relevant here is the more frequent finding of an ischaemic aetiology and prior myocardial infarction among patients with RBBB and ns IVCD, compared to patients with LBBB. Therefore, patients with RBBB and ns IVCD may have greater scar burden and, accordingly, less response to CRT.[21]

Whatever the doubts about the value of CRT in patients with non-LBBB morphology, it is clear these patients are at high risk and merit intervention to reduce this risk. Whether RBBB (and ns

IVCD) is merely a marker of severity of heart muscle disease or whether some other, targeted, intervention, in addition to optimal pharmacological treatment, might be beneficial in these patients is unknown. His bundle pacing might be such an approach, although this needs to be tested in appropriately designed prospective clinical trials. In patients with RBBB, right ventricular septal pacing can shorten QRS duration and this pacing modality achieved electrical resynchronization and improved left ventricular ejection fraction and heart failure symptoms in a study of patients with HFrEF and isolated RBBB.[22, 23,24]

Patients with ns IVCD are a potentially greater management problem, given the much larger number of such individuals. While there is no indication for CRT in these individuals *per se*, biventricular pacing/CRT provided a significant benefit over right ventricular pacing in an important clinical trial in patients with reduced left ventricular ejection fraction (≤50%) and atrio-ventricular block requiring permanent pacing.[24] A further and novel finding of the present study is about the incidence of new QRS widening, along with the predictors and consequences of this. We found that 16% of patients developed new-onset QRS-widening to ≥130 ms over a median follow-up of 2.7 years (6.1 per 100 patient-years). Incident LBBB occurred in 6.3% of patients (2.4 per 100 patient-years). New-onset QRS-widening, irrespective of QRS morphology, was associated with a much higher subsequent rate of fatal and non-fatal outcomes. There were several independent predictors of new-onset QRS-widening to ≥130 ms of which the strongest was a QRS duration of 110-129 ms, with new QRS-widening occurring at more than twice the overall rate (14.1 per 100 patient-years), which was also the case for incident LBBB (5.9 per 100 patient-years) in individuals with a baseline QRS duration of 110-129 ms.

We know of only one other moderately large study reporting the incidence of LBBB in patients HFrEF. Investigators in Hull, UK, described a cohort of 1418 newly referred outpatients with

HFrEF.[28] Among the 473 patients without a pacemaker or baseline LBBB who had a 12 lead ECG at one year, 49 were found to have new LBBB (approximately 10%)., This is clearly a considerably higher rate than in our study (2.4% per year). However, there are several explanations for this. Most importantly, in the prior report from Hull, BBB was defined as a QRS duration of ≥120 ms, as was conventional at the time and, secondly, the Hull patients were considerably older (mean 70.5 years versus 62.4 years) and more were in NYHA functional class III or IV (all predictors of BBB). There is also the possibility that the estimate of incidence of LBBB in the Hull study is less precise, given that it was based on 49 cases (compared with 495 in the present study). In another small Israeli single-center study, 178 patients with HFrEF were followed-up for a median of 30 months, and incident LBBB was identified in 14 patients (7.9%).[29] This is closer to our estimate, of an incidence of 6.3% over a median of 30 months. Consequently, we believe that it is reasonable assumption that our report gives the most robust estimate of clinically relevant incident LBBB in ambulatory HFrEF patients with generally mild symptoms. The clinical relevance is that QRS widening to ≥130 ms with a LBBB pattern is a potential indication for CRT implantation. Clearly, the question begged by our findings is whether an annual 12 lead ECG recording should be made in patients with HFrEF who have a mildly abnormal QRS width.

These findings have several important limitations. The analyses reported were not planned prospectively. QRS duration and morphology were investigator reported and it is likely that some patients might have been misclassified. The trial inclusion and exclusion criteria limit the generalizability of our findings and the duration of follow-up was limited. ECGs were only recorded at yearly intervals and, given the association of QRS widening with a greater risk of death, it is possible that more frequent ECG recording, and longer follow-up might have identified a higher incidence of LBBB and evidence of QRS widening.

In conclusion, even a “mildly abnormal” QRS duration (110-129 ms) identifies HFrEF patients at high risk. A significant proportion will progress to QRS duration ≥130 ms with a LBBB configuration and an indication for CRT. Advanced heart failure therapies may be considered in patients of this type with other QRS morphologies.

DISCLOSURES

Drs Kristensen, Castagno and Rørth report no conflict of interests. Dr Jhund reports consulting and speaker’s fees from Novartis and research funding from Boehringer Ingelheim. Dr Køber reports consulting fees from Novartis. Dr. McMurray´s employer, University of Glasgow, has received fees for his consulting or trial committee work with Abbvie, Amgen, AstraZeneca/Medimmune, Bayer, Bristol Myers Squibb, DalCor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Sanofi-Aventis and Stealth Therapeutics.

SOURCES OF FUNDING

Prof McMurray is supported by a British Heart Foundation Centre of Research Excellence Grant RE/18/6/34217.

REFERENCES

1. Grines CL, Marsalese DL, Brodie B, Griffin J, Donohue B, Costantini CR, Balestrini C, Stone G, Wharton T, Esente P, Spain M, Moses J, Nobuyoshi M, Ayres M, Jones D, Mason D, Sachs D, Grines LL and O'Neill W. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. PAMI-II Investigators. Primary Angioplasty in Myocardial Infarction. *Journal of the American College of Cardiology*. 1998;31:967-72.
2. Lund LH, Jurga J, Edner M, Benson L, Dahlstrom U, Linde C and Alehagen U. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *European heart journal*. 2013;34:529-39.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy P and Defibrillation in Heart Failure I. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England journal of medicine*. 2004;350:2140-50.
4. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L and Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *The New England journal of medicine*. 2005;352:1539-49.
5. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W and Investigators M-CT. Cardiac-resynchronization therapy for the prevention of heart-failure events. *The New England journal of medicine*. 2009;361:1329-38.
6. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL and Resynchronization-Defibrillation for Ambulatory Heart Failure Trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *The New England journal of medicine*. 2010;363:2385-95.
7. Hawkins NM, Wang D, McMurray JJ, Pfeffer MA, Swedberg K, Granger CB, Yusuf S, Pocock SJ, Ostergren J, Michelson EL, Dunn FG, Investigators C and Committees. Prevalence and prognostic impact of bundle branch block in patients with heart failure: evidence from the CHARM programme. *Eur J Heart Fail*. 2007;9:510-7.
8. Zannad F, Huvelle E, Dickstein K, van Veldhuisen DJ, Stellbrink C, Kober L, Cazeau S, Ritter P, Maggioni AP, Ferrari R and Lechat P. Left bundle branch block as a risk factor for progression to heart failure. *Eur J Heart Fail*. 2007;9:7-14.
9. Lee SJ, McCulloch C, Mangat I, Foster E, De Marco T and Saxon LA. Isolated bundle branch block and left ventricular dysfunction. *J Card Fail*. 2003;9:87-92.
10. McMurray JJ, Krum H, Abraham WT, Dickstein K, Kober LV, Desai AS, Solomon SD, Greenlaw N, Ali MA, Chiang Y, Shao Q, Tarnesby G, Massie BM and Investigators AC. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. *The New England journal of medicine*. 2016;374:1521-32.
11. Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJ, Desai A, Gimpelewicz C, Kandra A, Reimund B, Rattunde H, Armbrecht J and Investigators A. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE (ATMOSPHERE) study. *Eur J Heart Fail*. 2011;13:107-14.
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau J, Shi VC, Solomon SD, Swedberg K, Zile MR, Committees P-H and Investigators. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2013;15:1062-73.
13. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR and Investigators P-HC. Baseline characteristics and treatment of patients in

Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). *Eur J Heart Fail*. 2014;16:817-25.
14. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *The New England journal of medicine*. 2014;371:993-1004.
15. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *NEnglJ Med*. 1991;325:293-302.
16. Cannon JA, Collier TJ, Shen L, Swedberg K, Krum H, Van Veldhuisen DJ, Vincent J, Pocock SJ, Pitt B, Zannad F and McMurray JJ. Clinical outcomes according to QRS duration and morphology in the Eplerenone in Mild Patients: Hospitalization and SurvIval Study in Heart Failure (EMPHASIS-HF). *Eur J Heart Fail*. 2015;17:707-16.
17. Reil JC, Robertson M, Ford I, Borer J, Komajda M, Swedberg K, Tavazzi L and Bohm M. Impact of left bundle branch block on heart rate and its relationship to treatment with ivabradine in chronic heart failure. *Eur J Heart Fail*. 2013;15:1044-52.
18. Abdel-Qadir HM, Tu JV, Austin PC, Wang JT and Lee DS. Bundle branch block patterns and long-term outcomes in heart failure. *International journal of cardiology*. 2011;146:213-8.
19. Baldasseroni S, Gentile A, Gorini M, Marchionni N, Marini M, Masotti G, Porcu M, Maggioni AP and Italian Network on Congestive Heart Failure I. Intraventricular conduction defects in patients with congestive heart failure: left but not right bundle branch block is an independent predictor of prognosis. A report from the Italian Network on Congestive Heart Failure (IN-CHF database). *Ital Heart J*. 2003;4:607-13.
20. Sohaib SM, Finegold JA, Nijjer SS, Hossain R, Linde C, Levy WC, Sutton R, Kanagaratnam P, Francis DP and Whinnett ZI. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. *JACC Heart failure*. 2015;3:327-36.
21. Leyva F, Foley PW, Chalil S, Ratib K, Smith RE, Prinzen F and Auricchio A. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2011;13:29.
22. Giudici MC, Abu-El-Haija B, Schrumpf PE, Bhave PD, Al Khiami B and Barold SS. Right ventricular septal pacing in patients with right bundle branch block. *J Electrocardiol*. 2015;48:626-9.
23. Sharma PS, Naperkowski A, Bauch TD, Chan JYS, Arnold AD, Whinnett ZI, Ellenbogen KA and Vijayaraman P. Permanent His Bundle Pacing for Cardiac Resynchronization Therapy in Patients With Heart Failure and Right Bundle Branch Block. *Circ Arrhythm Electrophysiol*. 2018;11:e006613.
24. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS and Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block Trial I. Biventricular pacing for atrioventricular block and systolic dysfunction. *The New England journal of medicine*. 2013;368:1585-93.
25. Carson P, Anand I, O'Connor C, Jaski B, Steinberg J, Lwin A, Lindenfeld J, Ghali J, Barnet JH, Feldman AM and Bristow MR. Mode of death in advanced heart failure: the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial. *Journal of the American College of Cardiology*. 2005;46:2329-34.
26. Kashani A and Barold SS. Significance of QRS complex duration in patients with heart failure. *Journal of the American College of Cardiology*. 2005;46:2183-92.
27. Sandhu R and Bahler RC. Prevalence of QRS prolongation in a community hospital cohort of patients with heart failure and its relation to left ventricular systolic dysfunction. *The American journal of cardiology*. 2004;93:244-6.
28. Clark AL, Goode K and Cleland JG. The prevalence and incidence of left bundle branch block in ambulant patients with chronic heart failure. *Eur J Heart Fail*. 2008;10:696-702.
29. Rav-Acha M, Nujidat A, Farkash R, Medina A, Ilan M, Klutstein M, Butnaru A, Weitsman T, Glikson M and Hasin T. Delayed prolongation of the QRS interval in patients with left ventricular dysfunction. *International journal of cardiology*. 2019;296:71-75.

Table 1: Baseline characteristics according to QRS duration and morphology (in those with QRS≥130ms)

	According to QRS duration				According to morphology in pts with QRS ≥130 ms			
	<110 ms	110-129 ms	≥130 ms	p-value	ns IVCD	RBBB	LBBB	p-value
No. patients	6,506	2,588	1,226		454	524	1789	
Age (years)	62.2 (12.0)	63.0 (11.5)	65.2 (11.3)	<0.001	63.9 (12.4)	65.4 (11.3)	65.5 (11.0)	0.026
Female sex	1649 (25%)	446 (17%)	697 (25%)	<0.001	89 (20%)	69 (13%)	539 (30%)	<0.001
Region				<0.001				<0.001
North America	161 (3%)	61 (2%)	87 (3%)		16 (4%)	18 (3%)	53 (3%)	
Latin America	1104 (17%)	484 (19%)	595 (22%)		73 (16%)	112 (21%)	410 (23%)	
Western Europe	1060 (16%)	527 (20%)	670 (24%)		104 (23%)	116 (22%)	450 (25%)	
Central Europe	2325 (36%)	879 (34%)	831 (30%)		134 (30%)	148 (28%)	549 (31%)	
Asia-Pacific	1856 (28%)	637 (25%)	584 (21%)		127 (28%)	130 (25%)	327 (18%)	
Systolic BP (mmHg)	124 (17)	123 (17)	122 (17)	<0.001	122 (16)	122 (17)	123 (17)	0.45
Heart rate (bpm)	74 (13)	72 (12)	71 (12)	<0.001	71 (12)	71 (12)	71 (11)	0.66
BMI (kg/m^2)	28 (6)	28 (5)	27 (5)	0.065	27 (5)	28 (5)	27 (5)	0.66
eGFR (mL/min/1.73 m^2)	72 (59, 86)	71 (59, 84)	69 (56, 82)	<0.001	70 (57, 84)	67 (56, 81)	69 (56, 82)	0.23
Chronic kidney disease*	1700 (26%)	690 (27%)	856 (31%)	<0.001	130 (29%)	165 (32%)	561 (31%)	0.51
Ischaemic HF aetiology	3750 (58%)	1487 (58%)	1503 (54%)	0.0095	283 (63%)	335 (64%)	882 (49%)	<0.001

Time since diagnosis of HF				<0.001				0.65
<1 year	2664 (41%)	856 (33%)	834 (30%)		145 (32%)	162 (31%)	527 (30%)	
1-5 years	2476 (38%)	974 (38%)	1055 (38%)		161 (36%)	204 (39%)	690 (39%)	
>5 years	1363 (21%)	757 (29%)	878 (32%)		148 (33%)	158 (30%)	572 (32%)	
LV ejection fraction (%)	30 (6)	28 (5)	27 (5)	0.065	29 (6)	30 (6)	28 (6)	<0.001
NT-proBNP (pg/ml)	1310 (720, 2509)	1455 (787,2919	1571 (821, 3099)	<0.001	1361 (710, 2847)	1560 (813, 3077)	1641 (849, 3199)	0.014
KCCQ CSS	79 (61, 92)	79 (63, 92)	81 (64, 92)	0.033	82 (66, 92)	81 (64, 93)	80 (64, 92)	0.72
NYHA Class				0.0012				0.73
I	282 (4%)	108 (4%)	86 (3%)		17 (4%)	20 (4%)	49 (3%)	
II	4458 (69%)	1755 (68%)	1974 (71%)		320 (71%)	377 (72%)	1277 (71%)	
III	1723 (27%)	689 (27%)	678 (25%)		110 (24%)	121 (23%)	447 (25%)	
IV	42 (1%)	32 (1%)	27 (1%)		6 (1%)	5 (1%)	16 (1%)	
Hypertension	4470 (69%)	1783 (69%)	1762 (64%)	<0.001	283 (62%)	327 (62%)	1152 (64%)	0.57
Diabetes	2050 (32%)	787 (30%)	827 (30%)	0.25	135 (30%)	184 (35%)	508 (28%)	0.012
Atrial fibrillation (history)	2425 (37%)	826 (32%)	814 (29%)	<0.001	148 (33%)	190 (36%)	476 (26%)	<0.001
Atrial fibrillation (ECG)	2004 (31%)	609 (24%)	524 (19%)	<0.001	95 (21%)	135 (26%	294 (16%)	<0.001
Prior HF hospitalization	3174 (49%)	1268 (49%)	1270 (46%)	0.025	201 (44%)	248 (47%)	821 (46%)	0.63
Prior myocardial Infarction	2500 (38%)	1085 (42%)	1081 (39%)	0.0082	225 (50%)	257 (49%)	599 (34%)	<0.001

Prior stroke	477 (7%)	216 (8%)	199 (7%)	0.19	31 (7%)	47 (9%)	121 (7%)	0.22
Beta blockers	6013 (92%)	2381 (92%)	2498 (90%)	0.0024	407 (90%)	471 (90%)	1620 (91%)	0.78
MRAs	2968 (46%)	1217 (47%)	1284 (46%)	0.45	210 (46%)	235 (45%)	839 (47%)	0.71
Diuretics	5068 (78%)	2092 (81%)	2244 (81%)	0.002	369 (81%)	435 (83%)	1440 (81%)	0.43
Digoxin	2116 (33%)	772 (30%)	866 (31%)	0.040	137 (30%)	163 (31%)	566 (32%)	0.83

ACE-I = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; HF = heart failure, ARB = angiotensin receptor blocker; BMI = body mass index; Chronic kidney disease = eGFR<60 ml/min/1.73m^2 eGFR = estimated glomerular filtration rate; HF = Heart Failure; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MLHF = Minnesota Living with Heart Failure questionnaire; MRA = mineralocorticoid-receptor antagonist; NYHA = New York Heart Association; RVEF = right ventricular ejection fraction SBP = systolic blood pressure

Table 2: Risk of adverse outcomes according to baseline ECG

	No. events/patients	Crude rate per 100 py	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
Primary composite						
Normal QRS duration (<110 ms)	1543/6506	9.6	1.00 (Ref)		1.00 (Ref)	
QRS 110-129 ms	826/2588	13.6	1.42 (1.30-1.54)	<0.001	1.35 (1.23-1.47)	
QRS ≥130 ms	937/2767	14.7	1.53 (1.41-1.66)	<0.001	1.44 (1.32-1.57)	<0.001
QRS ≥130 ms + nsIVCD	168/454	16.9	1.75 (1.49-2.05)	<0.001	1.65 (1.40-1.94)	<0.001
QRS ≥130 ms + RBBB	187/524	16.0	1.66 (1.42-1.93)	<0.001	1.54 (1.31-1.79)	<0.001
QRS ≥130 ms + LBBB	582/1789	13.9	1.44 (1.31-1.59)	<0.001	1.36 (1.23-1.50)	<0.001
HF hospitalization						
Normal QRS duration (<110 ms)	786/6506	4.9	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001
QRS 110-129 ms	441/2588	7.3	1.48 (1.32-1.66)	<0.001	1.40 (1.24-1.58)	<0.001
QRS ≥130 ms	520/2767	8.2	1.66 (1.48-1.85)	<0.001	1.56 (1.39-1.75)	<0.001
QRS ≥130 ms + nsIVCD	91/454	9.1	1.84 /1.48-2.29)	<0.001	1.74 (1.39-2.17)	<0.001
QRS ≥130 ms + RBBB	111/524	9.5	1.92 (1.57-2.34)	<0.001	1.73 (1.41-2.13)	<0.001
QRS ≥130 ms + LBBB	318/1789	7.6	1.54 (1.35-1.76)	<0.001	1.46 (1.27-1.67)	<0.001
Cardiovascular death						
Normal QRS duration (<110 ms)	1028/6506	6.0	1.00 (Ref)		1.00 (Ref)	
QRS 110-129 ms	574/2588	8.7	1.45 (1.31-1.61)	<0.001	1.39 (1.25-1.54)	<0.001
QRS ≥130 ms	638/2767	8.4	1.51 (1.36-1.66)	<0.001	1.39 (1.26-1.55)	<0.001
QRS ≥130 ms + nsIVCD	106/454	9.4	1.56 (1.28-1.91)	<0.001	1.46 (1.19-1.79)	<0.001
QRS ≥130 ms + RBBB	126/524	9.7	1.62 (1.35-1.95)	<0.001	1.48 (1.23-1.79)	<0.001
QRS ≥130 ms + LBBB	406/1789	8.8	1.46 (1.30-1.64)	<0.001	1.35 (1.19-1.52)	<0.001
All-cause mortality						
Normal QRS duration (<110 ms)	1234/6506	7.2	1.00 (Ref)		1.00 (Ref)	
QRS 110-129 ms	667/2588	10.1	1.41 (1.28-1.55)	<0.001	1.35 (1.22-1.48)	<0.001
QRS ≥130 ms	740/2767	10.5	1.46 (1.33-1.59)	<0.001	1.33 (1.21-1.46)	<0.001
QRS ≥130 ms + ns IVCD	126/454	11.1	1.55 (1.29-1.86)	<0.001	1.45 (1.20-1.76)	<0.001
QRS ≥130 ms + RBBB	143/524	11.0	1.53 (1.29-1.82)	<0.001	1.37 (1.15-1.64)	<0.001
QRS ≥130 ms + LBBB	471/1789	10.2	1.41 (1.27-1.57)	<0.001	1.28 (1.15-1.44)	<0.001
Pump failure death						
Normal QRS duration (<110 ms)	192/6506	1.1	1.00 (Ref)		1.00 (Ref)	
QRS 110-129 ms	132/2588	2.0	1.79 (1.44-2.24)	<0.001	1.70 (1.36-2.14)	<0.001
QRS ≥130 ms	155/2767	2.2	1.96 (1.59-2.43)	<0.001	1.63 (1.30-2.03)	<0.001
QRS ≥130 ms + ns IVCD	25/454	2.2	1.98 (1.31-3.01)	0.001	1.73 (1.12-2.66)	0.013
QRS ≥130 ms + RBBB	38/524	2.9	2.63 (1.85-3.72)	<0.001	2.18 (1.53-3.13)	<0.001
QRS ≥130 ms + LBBB	92/1789	2.0	1.77 (1.38-2.27)	<0.001	1.44 (1.11-1.87)	0.006

Sudden cardiac death						
Normal QRS duration (<110 ms)	488/6506	2.8	1.00 (Ref)		1.00 (Ref)	
QRS 110-129 ms	260/2588	3.9	1.38 (1.19-1.61)	<0.001	1.33 (1.14-1.55)	<0.001
QRS ≥130 ms	281/2767	4.0	1.39 (1.20-1.62)	<0.001	1.37 (1.17-1.59)	<0.001
QRS ≥130 ms + ns IVCD	42/454	3.7	1.30 (0.95-1.78)	0.102	1.24 (0.90-1.71)	0.191
QRS ≥130 ms + RBBB	46/524	3.5	1.24 (0.91-1.67)	0.167	1.15 (0.84-1.57)	0.371
QRS ≥130 ms + LBBB	193/1789	4.2	1.46 (1.24-1.73)	<0.001	1.47 (1.23-1.76)	<0.001

Table 3: Risk of developing intraventricular conduction disorder according to QRS duration at baseline

	No. events/patients	Event rate per 100py	Unadjusted OR (95% CI)	P	Adjusted* OR (95% CI)	P
Any QRS ≥130 ms	1234/7888	6.1				
Baseline QRS <110 ms	511/5691	3.4	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110-129 ms	723/2197	14.1	4.97 (4.38-5.65)	<0.001	4.64 (4.07-5.28)	<0.001
QRS ≥130 ms ns IVCD	549/7888	2.7				
Baseline QRS <110 ms	264/5691	1.8	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110-129 ms	285/2197	5.5	3.06 (2.57-3.65)	<0.001	2.89 (2.41-3.46)	<0.001
QRS ≥130 ms RBBB	190/7888	0.9				
Baseline QRS <110 ms	75/5691	0.5	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110-129 ms	115/2197	2.1	4.14 (3.08-5.56)	<0.001	3.89 (2.87-5.27)	<0.001
QRS ≥130 ms LBBB	495/7888	2.4				
Baseline QRS <110 ms	172/5691	1.1	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110-129 ms	323/2197	5.9	5.53 (4.56-6.70)	<0.001	5.11 (4.20-6.23)	<0.001

Table 4: Baseline characteristics in patients with QRS <130 ms at baseline according to future QRS -widening in patients with one or more ECG performed during follow-up

	No QRS widening (>130 ms)	Any incident QRS widening during f-u	p-value	Incident nsIVCD	Incident RBBB	Incident LBBB	p-value
No. patients	6654	1234		549	190	495	
Age (years)	62 (12)	64 (11)	<0.001	61.7 (11.6)	65.5 (11.3)	64.8 (10.4)	<0.001
Female sex	1585 (24%)	237 (19%)	<0.001	96 (18%)	32 (17%)	109 (15%)	0.12
Region			<0.001				<0.001
North America	155 (2%)	44 (4%)		23 (4%)	8 (4%)	13 (3%)	
Latin America	1128 (17%)	232 (19%)		75 (14%)	36 (19%)	122 (25%)	
Western Europe	1104 (17%)	299 (24%)		135 (25%)	43 (23%)	121 (24%)	
Central Europe	2431 (36%)	379 (31%)		153 (28%)	60 (32%)	166 (34%)	
Asia-Pacific	1836 (28%)	280 (23%)		164 (30%)	43 (23%)	73 (15%)	
Systolic BP (mmHg)	124 (17)	124 (18)	0.52	124 (18)	124 (19)	124 (17)	0.83
Heart rate (bpm)	73 (13)	71 (13)	<0.001	71 (13)	72 (14)	71 (12)	0.24
BMI (kg/m^2)	28 (6)	28 (5)	0.84	28 (5)	28 (5)	28 (5)	0.17
eGFR (mL/min/1.73 m^2)	72 (59, 85)	71 (59, 85)	0.51	74 (61, 86)	68 (57, 84)	69 (58, 84)	0.006
Chronic kidney disease*	1713 (26%)	320 (26%)	0.89	122 (22%)	61 (32%)	137 (28%)	0.014

Ischaemic HF aetiology	3804 (57%)	740 (60%)	0.068	338 (62%)	126 (66%)	276 (56%)	0.024
Time since diagnosis of HF			<0.001				0.12
<1 year	2698 (41%)	404 (33%)		199 (36%)	58 (31%)	147 (30%)	
1-5 years	2485 (37%)	476 (39%)		204 (37%)	81 (43%)	191 (39%)	
>5 years	1468 (22%)	353 (29%)		146 (27%)	51 (27%)	156 (32%)	
LV ejection fraction (%)	30 (6)	29 (6)	<0.001	29 (6)	30 (6)	28 (5)	0.17
NT-proBNP (pg/ml)	1264 (702, 2364)	1365 (744, 2699)	0.0083	1335 (732, 2501)	1418 (770, 2837)	1390 (750, 2901)	0.3034
KCCQ CSS	80 (63, 92)	80 (65, 92)	0.58	81 (64, 92)	80 (63, 92)	80 (66, 91)	0.94
NYHA Class			0.050				0.82
I	304 (5%)	42 (3%)		19 (4%)	4 (2%)	19 (4%)	
II	4588 (69%)	896 (73%)		405 (74%)	142 (75%)	349 (71%)	
III	1709 (26%)	286 (23%)		121 (22%)	42 (22%)	123 (25%)	
IV	49 (1%)	9 (1%)		4 (1%)	1 (1%)	4 (1%)	
Hypertension	4607 (69%)	832 (67%)	0.21	357 (63%)	130 (68%)	355 (72%)	0.013
Diabetes	2049 (31%)	395 (32%)	0.40	175 (32%)	56 (30%)	164 (33%)	0.65
Atrial fibrillation (history)	2450 (37%)	388 (31%)	<0.001	158 (29%)	74 (39%)	156 (32%)	0.034
Atrial fibrillation (ECG)	1994 (30%)	292 (24%)	<0.001	108 (20%)	59 (31%)	125 (25%)	0.004
Prior HF hospitalization	3264 (49%)	574 (47%)	0.10	253 (46%)	82 (43%)	239 (48%)	0.47

Prior myocardial Infarction	2557 (38%)	547 (44%)	<0.001	258 (47%)	100 (53%)	189 (38%)	<0.001
Prior stroke	520 (8%)	81 (7%)	0.13	40 (7%)	11 (6%)	30 (6%)	0.65
Beta blockers	6180 (93%)	1124 (91%)	0.027	496 (90%)	177 (93%)	451 (91%)	0.50
MRAs	3072 (46%)	550 (45%)	0.30	243 (44%)	84 (44%)	223 (45%)	0.96
Diuretics	5184 (78%)	997 (81%)	0.024	434 (79%)	151 (80%)	412 (83%)	0.20
Digoxin	2107 (32%)	363 (29%)	0.12	146 (27%)	56 (30%)	161 (33%)	0.11

Table 5 Predictors of incident QRS widening >130ms during follow-up (irrespective of morphology

	Univariate model OR (95% CI)	**P**	**Multivariable model OR (95% CI)**	**P**
QRS 110-129 vs <110 ms	4.97 (4.39-5.65)	<0.001	4.55 (3.98-5.19)	<0.001
Age per 5y increase	1.05 (1.02-1.08)	<0.001	1.06 (1.03-1.10)	0.001
Men vs. women	1.32 (1.13-1.53)		1.13 (0.95-1.34	0.155
HF duration				
1-5 years vs <1 year	1.61 (1.37-1.88)	<0.001	1.23 (1.05-1.44)	0.009
>5 years vs < 1 year	1.28 (1.11-1.48)	0.001	1.29 (1.08-1.54)	0.004
NYHA III-IV vs. I-II	1.14 (0.99-1.31)	0.067	1.14 (0.98-1.34)	0.091
LVEF per 1% decrease	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001
Pulse, per 5 bpm decrease	1.09 (1.06-1.12)	<0.001	1.06 (1.02-1.09)	<0.001
SBP per 5 mmHg decrease	0.99 (0.98-1.01)	0.524	0.99 (0.97-1.01)	0.277
BMI per 1 unit increase	1.00 (0.99-1.01)	0.84	1.01 (0.99-1.02)	0.236
NT-proBNP per 100 pg/ml increase	1.00 (1.00-1.00)	0.388	1.00 (1.00-1.00)	0.586
eGFR, per 5 unit increase	0.99 (9,98-1.01)	0.314	1.01 (1.00-1.03)	0.109
Atrial fibrillation	0.79 (0.69-0.90)	<0.001	0.88 (0.75-1.02)	0.093
Prior MI	1.28 (1.13-1.44)	<0.001	1.14 (0.99-1.31)	0.077
Prior Stroke	0.83 (0.65-1.06)	0.129	0.77 (0.59-1.00)	0.048
Prior HF hospitalization	0.90 (0.80-1.02)	0.101	0.93 (0.82-1.07)	0.318
Diabetes	1.06 (0.93-1.21)	0.396	1.07 (0.92-1.23)	0.377

Table 6: Outcomes after incident QRS widening (≥130ms)

	No. events/ patients	Crude rate per 100py	Adjusted HR (95% CI)	P
Any incident QRS≥130ms				
Primary composite				
No incident QRS≥130ms	1453/7888	7.4	1.00 (ref.)	
Any incident QRS≥130ms	196/880	13.9	1.49 (1.25-1.76)	<0.001
All-cause mortality				
No incident QRS≥130ms	905/7888	4.4	1.00 (ref.)	
Any incident QRS≥130ms	170/988	13.0	1.69 (1.43-2.00)	<0.001
Incident nsIVCD				
Primary composite				
No incident nsIVCD	1548/7888	7.7	1.00 (ref.)	
Incident ns IVCD	62/373	13.4	1.50 (1.16-1.95)	0.002
All-cause mortality				
No incident nsIVCD	1004/7888	4.7	1.00 (ref.)	
Incident nsIVCD	71/415	13.7	1.88 (1.47-2.40)	<0.001
Incident RBBB				
Primary composite				
No incident RBBB	1585/7888	7.7	1.00 (ref)	
Incident RBBB	25/149	13.3	1.34 (0.90-1.99)	0.15
All-cause mortality				
No incident RBBB	1047/7888	4.8	1.00 (ref.)	
Incident RBBB	28/168	12.7	1.51 (1.04-2.21)	0.032
Incident LBBB				
Primary composite				
No incident LBBB	1540/7888	7.6	1.00 (ref.)	
Incident LBBB	70/358	14.7	1.42 (1.12-1.82)	0.005
All-cause mortality				
No incident LBBB	1088/7888	4.7	1.00 (ref.)	
Incident LBBB	71/405	12.4	1.42 (1.11-1.81)	0.005

Figure 1: Flowchart of the study population

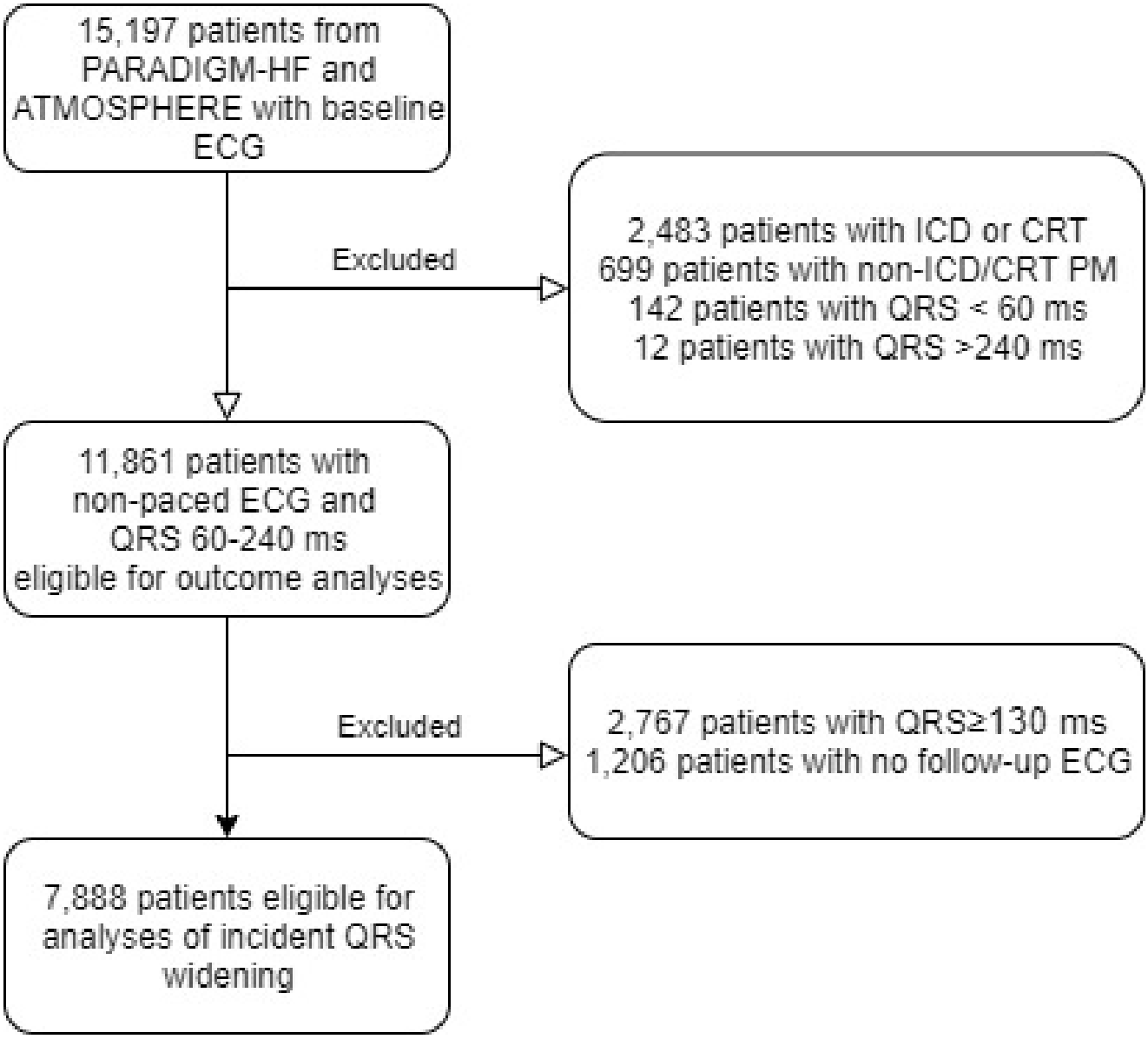


Figure 2: Cumulative incidence of study outcomes according to baseline QRS duration and morphology.

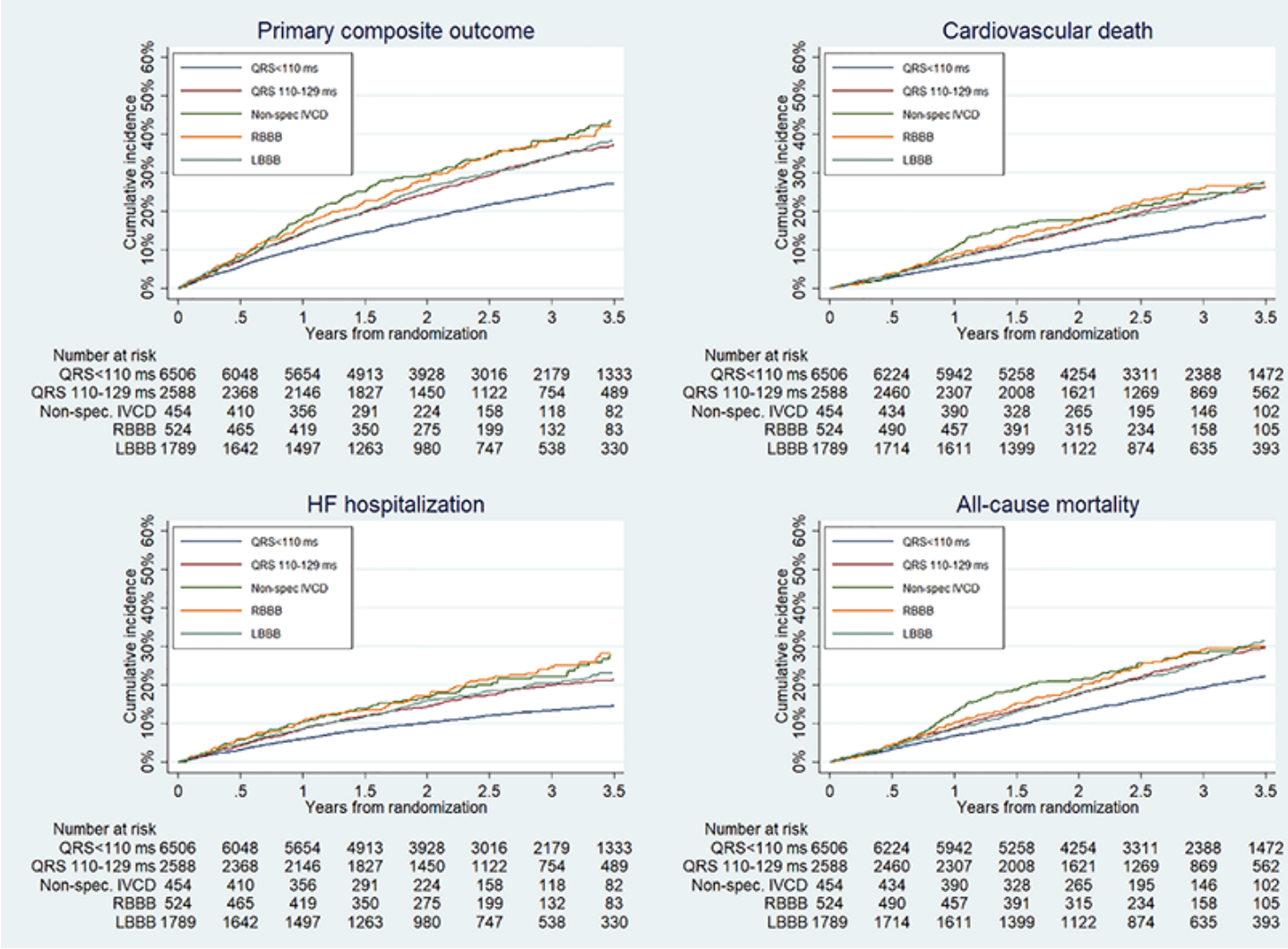
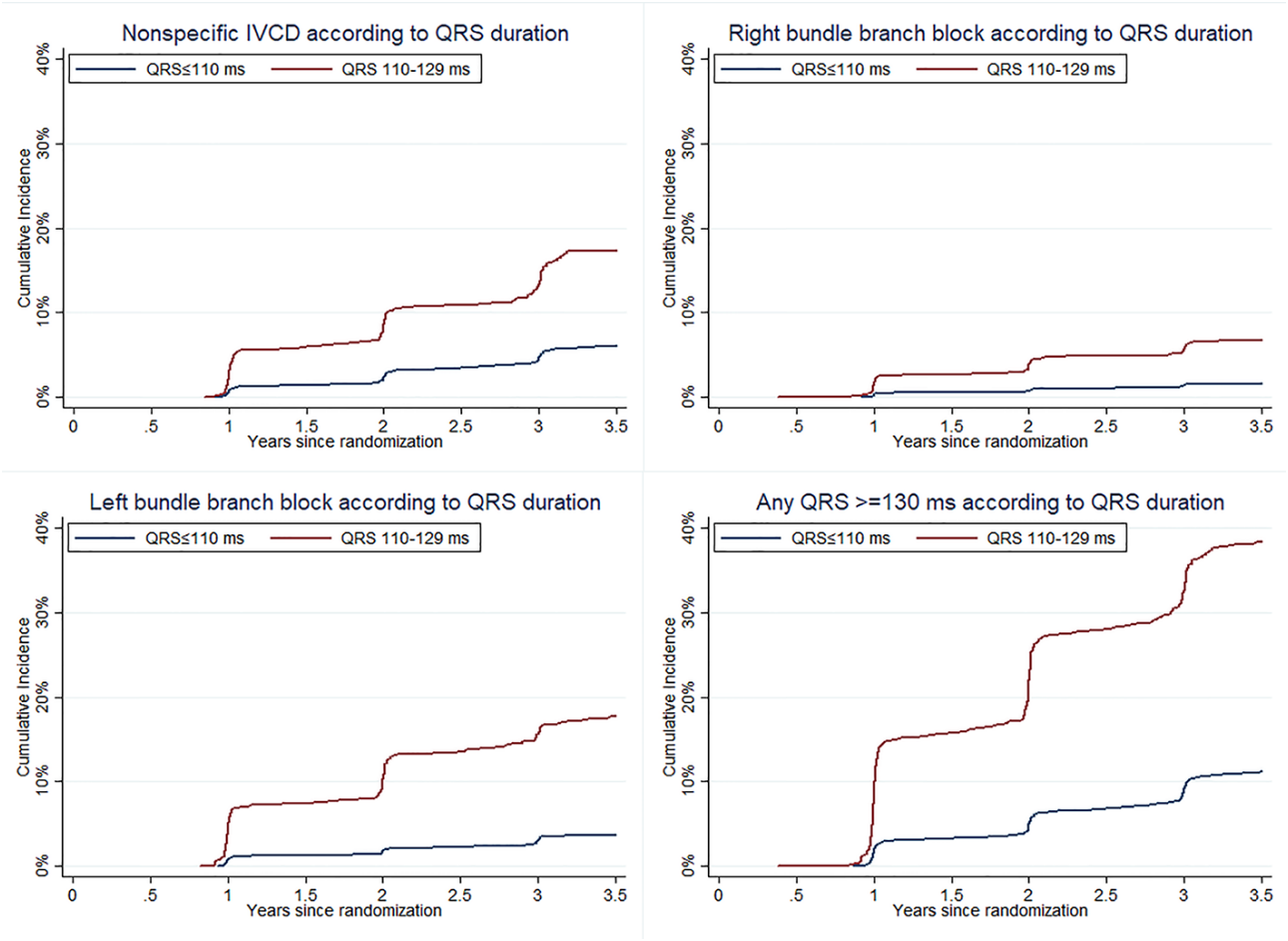


Figure 3: Cumulative incidence of nsIVCD (A) and incident RBBB (B) incident LBBB (C) and any QRS ≥130ms (D)



APPENDIX

Supplementary Figure 1: Continuous relation between QRS duration and outcomes irrespective of morphology.